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INTERNATIONAL PRELIMINARY EXAMINATION REPORT
(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 45279/JMDMR	FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/PEA/416)	
International application No. PCT/GB 03/04744	International filing date (day/month/year) 04.11.2003	Priority date (day/month/year) 04.11.2002
International Patent Classification (IPC) or both national classification and IPC C07K14/705		
Applicant NATIONAL BLOOD SERVICE		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 6 sheets, including this cover sheet.
- ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).
- These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the opinion
- II ☐ Priority
- III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☐ Certain observations on the international application

Date of submission of the demand 19.05.2004	Date of completion of this report 10.12.2004
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**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. **PCT/GB 03/04744**

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I. Basis of the report

1. With regard to the elements of the international application (*Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*):

Description, Pages

1-27 as originally filed

Sequence listings part of the description, Pages

1-14 received on 25.02.2004 with letter of 20.02.2004

Claims, Numbers

1-24 as originally filed

Drawings, Sheets

1-11 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☒ furnished subsequently to this Authority in written form.

- ☒ furnished subsequently to this Authority in computer readable form.

- ☒ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☒ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

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5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 11-13, 15-22 (in part)

because:

☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (specify):

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the said claims Nos. 11-13, 15-22 (in part)

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the Standard.

☐ the computer readable form has not been furnished or does not comply with the Standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	11-22
	No: Claims	1-10,23,24
Inventive step (IS)	Yes: Claims	11-22
	No: Claims	1-10,23,24
Industrial applicability (IA)	Yes: Claims	1-24
	No: Claims	-

2. Citations and explanations

see separate sheet

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Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability;
citations and explanations supporting such statement

Reference is made to the following documents:

- D1: SPRING FRANCES A ET AL: "Intercellular adhesion molecule-4 binds $\alpha_4\beta_1$ and α_V -family integrins through novel integrin-binding mechanisms" BLOOD, vol. 98, no. 2, 15 July 2001 (2001-07-15), pages 458-466, XP002273536 ISSN: 0006-4971
- D2: BAILLY P ET AL: "THE LW BLOOD GROUP GLYCOPROTEIN IS HOMOLOGOUS TO INTERCELLULAR ADHESION MOLECULES" PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF USA, NATIONAL ACADEMY OF SCIENCE. WASHINGTON, US, vol. 91, no. 12, 7 June 1994 (1994-06-07), pages 5306-5310, XP002013399 ISSN: 0027-8424
- D4: HERMAND PATRICIA ET AL: "Binding sites of leukocyte beta2 integrins (LFA-1, Mac-1) on the human ICAM-4/LW blood group protein" JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 275, no. 34, 25 August 2000 (2000-08-25), pages 26002-26010, XP002273537 ISSN: 0021-9258

The application teaches a site-directed mutagenesis study on residues from ICAM-4 which, according to the predicted three-dimensional structure, are surface-exposed. The application also provides the identification of those residues which are involved in binding to $\alpha_4\beta_1$ and α_V -family integrins (F18, W19, V20 on A strand; K118 on the B-strand; W77 and L80 on the F-strand; R92, A94, T95, S96 and R97 on the G-strand and W66, N160, V161 and T162 on E strand). Several epitopes and footprints comprising some of the above residues are proposed which might be required for integrin binding. Based on the sequence of said epitopes, four antagonistic peptides have been identified (SEQ ID NO:9-11 and 13) which inhibit erythroblast and neutrophil adhesion to ICAM-4.

D1 discloses the predicted 3D-structure of ICAM-4 derived by molecular modelling from the known crystallographic structure on the crystal structure of ICAM-2 (see figure 2 and page 460, left-hand column last paragraph - left column, third paragraph). The predicted

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3D structure of ICAM-4 implicitly contains all the different epitopes and footprint domains which have been identified in the present application as being involved in binding to $\alpha_4\beta_1$ and α_V -family integrins and which are the object of claims 1-10. Therefore, the contents of D1 anticipate the subject-matter of **claims 1-10**.

D2 provides a model of the 3D structure of ICAM-4 based on the crystal structure of ICAM-2 and identifies the different strands and domains as in the present application (see figure 1). Therefore, this document also takes away the novelty of **claims 1-10**, since the different epitopes and footprint domains embraced by the claims are also implicitly present in the predicted 3D structure disclosed in this document.

It could be alleged that the tridimensional structure of the ICAM-4 as described in D1 and D2 merely consists of an array of overlapping potential antigenic determinants which lacks any information about which regions are important for binding to the $\alpha_4\beta_1$ and α_V -family integrins. However, the fact is that the three-dimensional structure of ICAM-4 was already known in the prior art, and that said structure contains, even if not yet characterised, all the epitopes which are responsible for binding to the different ICAM-4-substrates. The fact that the applicant have identified for the first time the amino acids that form said epitope does not change the fact that the epitope had already been made available as a region within a larger structure. Thus, the contents of D1 and D2 contain an implicit disclosure of the epitopes of claims 1-10.

The antagonistic peptides defined by SEQ ID NO:9-11 and 13 have not been disclosed in the prior art. In addition, D2, which can be considered as the closest prior art, provides anti-ICAM-4 antibodies which act as ICAM-4 antagonists in a binding assay of Fc-ICAM-4 to the β_2 integrins LFA-1 and Mac-1 (see figure 5). The document differs from the subject-matter of claims 11-22 in that the ICAM-4 antagonists are the peptides of SEQ ID NO:9-11 and 13, with the corresponding technical effect that the antagonists are able to prevent adhesion of ICAM-4 to integrins of the $\alpha_4\beta_1$ and the α_V families. Thus, the problem to be solved by the present application is the provision of alternative ICAM-4 antagonist able to block the interaction of ICAM-4 with integrins of the $\alpha_4\beta_1$ and α_V families. The skilled person, when posed with the above problem, would not be able to arrive to the peptides identified in the present invention, since D2 does not even suggest that the adhesive activity of ICAM-4 could be antagonised with peptides derived from the binding sites instead of with anti-ICAM-4 antibodies. Even if D1 shows that the binding of ICAM-4

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to cells is mediated through interactions with $\alpha_4\beta_1$ and α_V integrins (see figure 5), there is no indication in this document that said interaction could be prevented with peptides derived from the structure of ICAM-4. Therefore, the skilled person would not be able to arrive at the antagonistic peptides defined in the claims when considering the teaching of D1 and D2. Thus the subject-matter of claims which relate to the antagonistic peptides of SEQ ID NO:9-11 and 13 (**claims 11-14**), as well as all other claims relating to the uses of said peptides for antagonising the ICAM-4 epitopes or for medical purposes (**claims 15-22**) involve an inventive step.

D3 teaches the sequence of the cDNA coding for ICAM-4 (see figure 2). This cDNA encodes the epitopes and footprint domains of claims 1-10 and therefore, it anticipates the subject-matter of **claims 23 and 24**, as far as it relates to nucleic acid coding for the epitopes or footprints of claims 1-10. It could be alleged that the cDNA provided in D3 encodes for the full-length ICAM-4, whereas the present claims relate to nucleic acids coding for the epitopes. However, due to the fact that the epitopes and footprint domains are formed by amino acids which are non-contiguous in the polypeptide chain, the nucleic acids encoding said epitopes must necessarily comprise sequences coding for the intervening regions between the amino acids which form the epitopes. In addition, claim 24 relates to the nucleic acid of SEQ ID NO:12, which corresponds to the sequence of the polynucleotide coding for the mature form of human ICAM-4, which is also disclosed in D3 (see the underlined part of the sequence in figure 2).

Other remarks

Claim 21 is not clear. It is not apparent how a disease which is related to a decreased binding of ICAM-4 could be treated with a compound which antagonises binding of ICAM-4 to its receptor, since it could be expected that such a compound would lead to an even stronger decrease in the levels of ICAM-4 binding.

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